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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
NICHOLS, CHRISTOPHER J

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 05/20/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/580,018	SCHENK ET AL.	
	Examin r	Art Unit	
	Christopher Nichols, Ph.D.	1647	

-- The MAILING DATE of this communication appears on the cover sheet with th correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 February 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-68* is/are pending in the application.

4a) Of the above claim(s) *42,43 and 47-68* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-41 and 44-46* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *4 6 11* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Election/Restriction

1. Applicant's election with **traverse** of Group I (claims 1-41 and 44-46) in Paper No. 11 is acknowledged. The traversal is on the ground(s) that the species are not mutually exclusive as in MPEP 806.04(f) and thus should not be restricted. This is persuasive. The species requirement as set forth in Paper No. 12 (12 March 2002) is hereby withdrawn. Claims **42, 43**, and **47-68** are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention and species, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 12. The restriction requirement is still deemed proper and is therefore made FINAL.

Sequence Requirements

2. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth below. This application discloses an amino acid sequence on Figures 19 and 20 without the appropriate SEQ ID NO. Correction is required.

Drawings

3. The drawings are objected to because Figure 10 contains two panels which must be labeled "10A" and "10B" in both the drawings and the specification. A proposed drawing correction or corrected drawings are required in reply to the Office action to avoid abandonment of the application. The objection to the drawings will not be held in abeyance.

4. The drawing of Figure 11 is objected to because the figure lacks an appropriate legend which indicates the peptide treatment groups as indicated and described in the figure and specification, see in particular pp. 62-63 and brief description of the drawings, p. 7. A proposed drawing correction or corrected drawings are required in reply to the Office action to avoid abandonment of the application. The objection to the drawings will not be held in abeyance. Applicants may alternatively choose to amend the brief description of the drawings so that it clearly reflects the groups represented in the Figure. Such amendment would be considered an appropriate correction so as to obviate abandonment of the application.

Information Disclosure Statement

5. The information disclosure statements filed 3 November 2000 (Paper No. 4), 8 January 2001 (Paper No. 6), and 18 February 2003 (Paper No. 18) contains particular references (**#144, #161, #174, #186, #220, #222, #223, #224, #304**) which fail to comply with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609 because they lack a relevant public availability date. Those references have been placed in the application file, but the information referred to therein has not been considered as to the merits. Applicant is advised that the date of any re-submission of any item of information contained in this information disclosure statement or the submission of any missing element(s) will be the date of submission for purposes of determining compliance with the requirements based on the time of filing the statement, including all certification requirements for statements under 37 CFR 1.97(e). See MPEP § 609 ¶ C(1).

Double Patenting

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

6. Claims **1-41** and **44-47** are provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims **1-2, 4-8,** and **10-24** of copending Application No. 09/322289. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

7. Claims **1-41** and **44-47** are provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims **1-23** and **26** of copending Application No. 09/580015. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

8. Claims **1-41** and **44-47** are provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims **1-46** of copending Application No. 09/724552. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

9. Claims **1-41** and **44-47** are provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims **1-41** of copending Application No. 09/724273. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

Non-Statutory Double Patenting Rejection

> The non-statutory double patenting rejection, whether of the obviousness-type or non-obviousness-type, is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent. In re Thorington, 418 F.2d 528, 163 USPQ 644 (CCPA 1969); In re Vogel, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); In re Van Ornum, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); In re Longi, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); and In re Goodman, 29 USPQ2d 2010 (Fed. Cir. 1993).
>
> A timely filed terminal disclaimer in compliance with 37 CFR 1.321(b) and (c) may be used to overcome an actual or provisional rejection based on a non-statutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.78(d).
>
> Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

10. Claims **1-41** and **44-47** are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims **42** and **43** of Application No. 09/497553. Although the conflicting claims are not identical, they are not patentably distinct from each other because instant claims are either anticipated by, or would have been obvious over the '553 claims. Both instant claims and the '533 claims are drawn to a use of an anti-Aβ antibody as a medicament for Alzheimer's. Instant claims recite administration of antibodies comprising antibodies immunospecific for Aβ as does the '553. Thus, it would have been *prima*

facie obvious to the skilled artisan that the claims in both instant and the '553 application would fully encompass treatment of Alzheimer's disease. This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

11. Claims **1-41** and **44-47** are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims **1-24, 28-32** and **36-37** of Application No. 09/724495. Although the conflicting claims are not identical, they are not patentably distinct from each other because instant claims are either anticipated by, or would have been obvious over the '495 claims. Both instant claims and the '495 claims are drawn to a use of an anti-Aβ antibody as a medicament for Alzheimer's disease including a step of immunizing the patient with an Aβ peptide and drawing the antibodies from said patient for *ex vivo* administration. Instant claims recite administration of antibodies comprising antibodies immunospecific for an epitope within residues 1-5 of Aβ as does the '495. Thus, it would have been *prima facie* obvious to the skilled artisan that the claims in both instant and the '495 application would fully encompass treatment of Alzheimer's disease. This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

12. Claims **1-41** and **44-47** are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims **1-47** of copending Application No. 09/979701. Although the conflicting claims are not identical, they are not patentably distinct from each other because instant claims are either anticipated by, or would have been obvious over the '701 claims. Both instant claims and the '495 claims are drawn to a use of an anti-Aβ antibody as a medicament for Alzheimer's disease including a step of immunizing the patient with an Aβ peptide and drawing the antibodies from said patient for *ex vivo* administration. Instant claims recite administration of antibodies comprising antibodies immunospecific for an epitope within residues 1-3, 1-4, 1-5, 1-6, 1-7, and 3-7 of Aβ as does the

'701. Thus, it would have been prima facie obvious to the skilled artisan that the claims in both instant and the '701 application would fully encompass treatment of Alzheimer's disease. This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

13. Claims **1-41** and **44-47** are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims **1-12, 14-15, 19-23,** and **26** of copending Application No. 09/724961. Although the conflicting claims are not identical, they are not patentably distinct from each other because instant claims are either anticipated by, or would have been obvious over the '961 claims. Both instant claims and the '961 claims are drawn to a use of an anti-Aβ antibody as a medicament for Alzheimer's disease. Instant claims recite administration of antibodies comprising anti-Aβ antibodies immunospecific for an epitope within residues 1-3, 1-4, 1-5, 1-6, 1-7, and 3-7 of Aβ which are species of the genus in the claims of '961 which are directed to an epitope within residues 1-12 of Aβ. Thus, it would have been prima facie obvious to the skilled artisan that the claims in both instant and the '961 application would fully encompass treatment of Alzheimer's disease. This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

14. Claims **1-41** and **44-47** are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for *treating Alzheimer's disease via administration of an*

anti-Aβ antibody immunospecific for an epitope within residues 1-3, 1-4, 1-5, 1-6, 1-7, or 3-7 of Aβ, does not reasonably provide enablement for *preventing or treating any disease associated with amyloid deposits, or any method of administering antibodies which bind other components of amyloid deposits.*. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected to make and use the invention commensurate in scope with these claims.

15. The instant invention is drawn to methods of treating amyloidogenic diseases comprising administration of an anti-Aβ antibody. The claims of the above invention are also drawn to methods of treating or preventing Down's syndrome or Alzhimer's Disease. Claims are presented which limited the antibody to those that bind an epitope within residues 1-3, 1-4, 1-5, 1-6, 1-7, or 3-7 of Aβ. The language of said claims encompasses both treatment and prevention.

16. The claims are drawn to a method for treatment and prevention of diseases associated with amyloid deposits of Aβ in the brain of a patient. The specification teaches that the administration of particular anti-Aβ antibodies is able to reduce β-amyloid levels within the brains of mice which are transgenic for PDAPP. These mice exhibit Alzheimer's type over production and build up of beta-amyloid within the brain. However, as recognized in the art, these mice do not exhibit Down's Syndrome or other amyloidogenic diseases, see in particular Schenk et al., Nature, 400:173-77, 1999 (**IDS**), Games et al., Nature 373(6514): 523-7, 1995 (**IDS**) and Chen et al., Progress in Br. Res., 117:327-34, 1998. Thus, the model system used is not recognized as providing for teachings that are predictive of the results which would be expected for the full scope of the claims. For example, the art recognizes that such *in vivo*

models are not readily correlated to the human *in vivo* case. In particular, the art teaches a lack of correlation of beneficial effects shown in the mouse model system in humans, see in particular Munch et al., J. Neural Transmission, 2002 July, 109(7-8): 1081-87. Specifically, treatments in involving the administration of Aβ peptide which were effective in mice were shown to evoke neurotoxicity when practiced in humans. Thus, for the aforementioned reasons treatment of all amyloidogenic diseases or a treatment regiment that includes Aβ peptide immunization does not appear to be commensurate in scope with the claims.

17. Moreover, the model system does not fairly teach that the treatment is effective to prevent the onset of disease. Alternatively the teachings exhibit how one can reduce the pathogenic characteristics of Alzheimer-like pathology but fails to teach the prevention of plaque development in animals. As evidence, the Examiner notes that all PDAPP mice exhibited plaques regardless of treatment regime. Even the most effective treatments were only effective to reduce the plaque burden in animals, not prevent it. The factors listed below have been considered in the analysis of enablement:

(A) The breadth of the claims;
(B) The nature of the invention;
(C) The state of the prior art;
(D) The level of one of ordinary skill;
(E) The level of predictability in the art;
(F) The amount of direction provided by the inventor;
(G) The existence of working examples; and
(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

18. The following references are cited herein to illustrate the state of the art of Alzheimer's disease treatment.

19. While the use of anti-Aβ antibodies is feasible for treating Alzheimer's disease, Sigurdsson *et al.* (November/December 2002) "A safer vaccine for Alzheimer's disease?" Neurobiology of Aging **23**(6): 1001-1008 teaches that the human Aβ gene used in the PDAPP mouse model differs in sequence from the murine counterpart. Therefore, the mouse models developing an immune reaction against a foreign, not endogenous form of Aβ, avoiding a possible autoimmune response (pp. 1003). The problem inherent in the instant application (especially claims 38 and 39) is that the Aβ as administrated is human and thus runs the risk of triggering an autoimmune response. Further Sigurdsson *et al.* (2002) teaches that the administration of Aβ to human patients leads to cerebral inflammation and may seed fibril or amyloid formation (pp. 1003).

20. In addition, Su *et al.* (6 February 1999) "Intravascular infusions of soluble β-amyloid compromise the blood-brain barrier, activate CNS glial cells and induce peripheral hemorrhage." Brain Research **818**(1): 105-117 teaches a study of rats administered twice daily with dosages of 50 mg/0.2 ml each of human $A\beta_{1-40}$ peptide (pp. 106; "*2.1 General protocol*"). The rats developed damage in their blood brain barrier (BBB) integrity, manifested by abnormal plasma protein exclusion/accumulation within and outside the cerebral vasculature (pp. 113). In addition, the rats infuse with the $A\beta_{1-40}$ peptide showed activated microglial and focal pulmonary hemorrhages (pp. 113 and Figure 2).

21. Also, a skilled artisan would be cautious of breaking autotolerance to stimulate a robust immune response to an endogenous protein as discussed by Münch and Robinson (2002) "Potential neurotoxic inflammatory responses to Aβ vaccination in humans." J. Neural Transm. **109**: 1081-1087 who teach that the administration of Aβ peptide can activate cytotoxic T-cells leading to collateral damage from a successful breaking of autotolerance to Aβ and a robust immune response against Aβ and Aβ containing plaques (pp. 1082-1083). Thus administration of the Aβ peptide can lead to unintended deleterious effects presenting the skilled artisan with a degree of unpredictability and teachings contrary to the invention as claimed.

22. Furthermore Furlan *et al.* (February 2003) "Vaccination with amyloid-β peptide induces autoimmune encephalomyelitis in C57/BL6 mice." Brain **126**(Pt. 2): 285-291 teaches that immunization of C57BL/6 mice with 100 μg of $A\beta_{1-42}$ using the schedule and protocol as set forth in Schenk *et al.* (1999) (**IDS**) lead to perivenular inflammatory encephalomyelitis (pp. 287).

23. Spooner *et al.* (13 December 2002) "The generation and characterization of potentially therapeutic Aβ antibodies in mice: differences according to strain and immunization protocol." Vaccine **21**(3-4): 290-297 teaches that the route of administration, the regiment of administration, and the genetic background of the mouse used affects the production of anti-Aβ antibodies in response to Aβ immunization (Table 1 and 2). It is also noted that although no deleterious effects were observed, this too could be dependent upon genetic factors of the animal receiving the immunization (pp. 296). Thus uncertainty is found by use of Aβ as an immungen in

regards to possible autoimmune reactions, general deleterious side effects, and variability in the production of anti-Aβ antibodies.

24. Finally, not only are overzealous immune responses a concern for the skilled artisan practicing the invention as claimed, but the possibility of a suppressed or hypoimmune response. Monsonego et al. (28 August 2001) "Immune hyporesponsiveness to amyloid β-peptide in amyloid precursor protein transgenic mice: Implications for the pathogenesis and treatment of Alzheimer's disease." PNAS **98**(18): 10273-10278 teaches that both humoral and cellular immune responses taper off after a succession of immunizations with Aβ (Figure 2 and 4). Monsonego et al. (2001) suggest that immune cells reactive to self-proteins may be selected against or destroyed by the host (pp. 10276-10277). Thus the skilled artisan is confronted with the unpredictability of whether or not the Aβ peptide immunization will trigger the desired immune response and contradictory prior art teaching away from the use of Aβ peptide immunizations, especially in humans.

25. Said claims are drawn very broadly to methods of treating or preventing any condition or disease suspected of being associated with amyloid deposits. Since the specification fails to provide any guidance for the successful treatment or prevention of such a broad range of diseases, and since resolution of the various complications in regards to targeting a particular amyloid deposit in an organism is highly unpredictable, one of skill in the art would have been unable to practice the invention without engaging in undue trial and error experimentation. In order to practice the invention using the specification and the state of the prior art as outlined above, the quantity of experimentation required to practice the invention as claimed *in vivo*

would require the *de novo* determination of formulations with acceptable toxicity and immunogenicity that are successfully delivered to target sites in appropriate cells and /or tissues. In the absence of any real guidance from the specification, the amount of experimentation would be undue, and one would have been unable to practice the invention over the scope claimed.

Summary

26. No claims are allowed.

27. The following publications were found by the Examiner during the prior art search and are of note:

a. US 2002/0094335 A1 (18 July 2002) Chalifour et al.

b. US 2002/0133001 A1 (19 September 2002) Gefter et al.

c. US 2002/0136718 A1 (26 September 2002) Raso

d. US 2002/0187157 A1 (12 December 2002) Jensen et al.

e. US 2003/0068325 A1 (10 April 2003) Wang

f. US 2003/0073655 A1 (17 April 2003) Chain

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Christopher James Nichols, Ph.D.** whose telephone number is 703-305-3955. The examiner can normally be reached on Monday through Friday, 8:00AM to 5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Gary Kunz, Ph.D.** can be reached on 703-308-4623. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications. The fax phone numbers for the customer service center is 703-872-9305

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Elizabeth C. Kemmerer

CJN
May 6, 2003

ELIZABETH KEMMERER
PRIMARY EXAMINER